

## Green Protocols for the Synthesis of Hydrazones

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### ABSTRACT

Green protocols for the synthesis of hydrazones by reacting hydrazine hydrate with different carbonyl compounds are investigated. The use of inexpensive, non-hazardous easily available stannous chloride dihydrate for the synthesis of hydrazones via solution reaction and grinding technique is reported. The structures of the synthesized compounds are established on the basis of physical, chemical and spectral data.

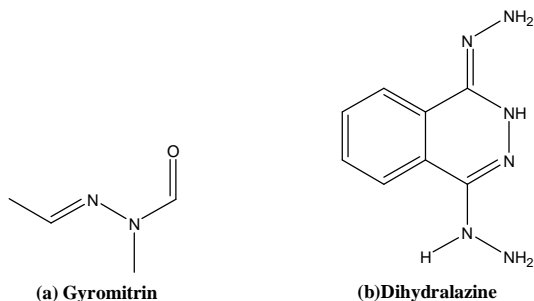
**Keywords:** Carbonyl compounds; Hydrazine hydrate; Hydrazones; Stannous Chloride Dihydrate; Grinding.

### INTRODUCTION

Hydrazones are the well known class of biologically active compounds in the field of synthetic chemistry. They possess antimicrobial<sup>1</sup>, antimalarial<sup>2</sup>, antitubercular,<sup>3,4</sup> anticonvulsant,<sup>5</sup> Anti HIV<sup>6</sup>, anti-inflammatory,<sup>7</sup> antihyperalgesic<sup>8</sup> and other pharmacological properties<sup>9-13</sup>.

In spite of these striking features one can see the glamour of hydrazones in the formation of complexes with various metals<sup>14-16</sup>. And these complexes are proving to be of great utility in pharmacy<sup>17</sup> and industries. With the need of time and adaptability hydrazones have been utilized as protecting groups for carbonyl compounds<sup>18</sup>.

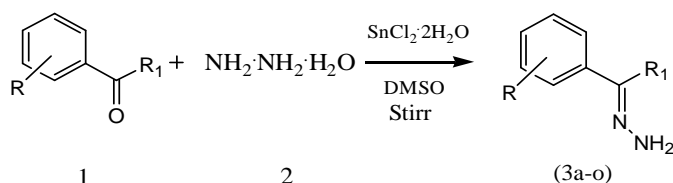
One more addition to the box of utilities is that hydrazones are an important class of chemical intermediate which can act as an electrophile and as nucleophile in mannich type reaction, asymmetric syncyanation, allylation reactions<sup>19</sup>. Hydrazones are also evolving as an interesting chapter in medical biotechnology via coupling methods. The hydrazones are used to couple with certain drugs. The hydrazone based bond is stable at neutral pH (in the blood) but acidic environment of lysosomes rapidly destroy the bond and the drug become free for its action<sup>20</sup>. Some hydrazones have been introduced as potent drugs such as Gyromitrin (a) is used as a toxin and Dihydralazine (b) as a hypertensive drug.



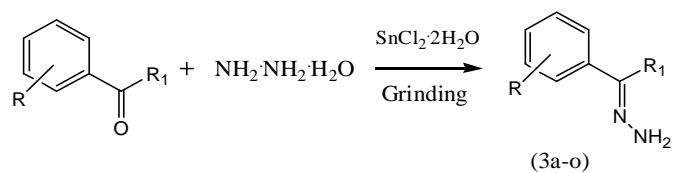
Classical method for the synthesis of hydrazones is the reaction of hydrazine with slight excess of carbonyl compounds in refluxing conditions using ethanol or toluene as a solvent. Recently RS Varma utilized the polystyrene sulphonic acid as a catalyst for the synthesis of hydrazones under microwave conditions<sup>21</sup>. DJ Brondani reported the synthesis of some aryl hydrazones in aqueous media under ultrasound irradiation<sup>22</sup>. And the very recent development in the synthetic methods is the use of Ball-Mill for the solvent free synthesis of hydrazones by F Lamaty<sup>19</sup>. The solid state reactions are observed to be

occurring efficiently and more selectively than solution reaction<sup>23</sup>, it might happen due to regular and tight arrangement of molecules in a crystal. In recent years,  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  is frequently used in organic synthesis<sup>24-26</sup> as a catalyst due to its properties such as nontoxic nature, easy availability, inexpensiveness and easiness for work up procedures. It played a great role for the synthesis of biologically active heterocycles such as benzimidazoles<sup>27</sup>, Quinoxalines<sup>28</sup> & functionalization of 4, 5-diaminopyrazoles<sup>29</sup>.

Hence for the fulfillment of green chemistry goals we offer a neat methodology for the synthesis of hydrazones. We have synthesized some hydrazones by reacting hydrazine hydrate with carbonyl compounds using stannous chloride dihydrate as a cheap and non-hazardous catalyst within few minutes. The reaction was carried out in the presence of DMSO as a solvent media as well as under solvent free conditions via grinding technique.



**Scheme 1.** Synthesis of hydrazones



**Scheme 2.** Synthesis of hydrazones via grinding technique

## RESULTS AND DISCUSSION

A series of hydrazones was synthesized employing green protocols. A variety of methods have been reported by researchers for the synthesis of hydrazones that includes longer reaction time, expensive catalytic systems, perilous solvents and tiresome work up procedures.

The present methods follow the principle of green chemistry and the use of inexpensive, non-hazardous stannous chloride dihydrate as a catalyst. The promising feature of this reaction is short reaction time (within 2-5) minutes, excellent yield and aqueous work up procedure. In addition to this grinding technique creates swift in the reaction conditions.

Applicability of the reaction with respect to carbonyl compounds was evaluated by reacting variety of ortho hydroxy acetophenones and ortho hydroxy aldehydes with hydrazine hydrate. Providentially we observed the rapid conversion of reactants in to products in case of both aldehydes and ketones. All the halogenated 2-hydroxy substituted aldehydes and ketones responded well producing the hydrazones with high purity.

For the optimization and evaluation of efficiency of the catalyst we studied the reaction with different mole ratios of catalyst. We observed that only 0.1 mmol of catalyst was ample evidence for the fruitful completion of reaction. On escalating up the quantity of catalyst we did not observed any remarkable effect on the reaction parameters. The data for the catalytic evolution is summarized in Table-2.

### General procedure for the synthesis of hydrazones

**Method A:** To a mixture of o-hydroxy acetophenones (0.01 mol) and hydrazine

hydrate (0.02 mol) in DMSO was added a catalytic amount of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ . The reaction mixture was stirred for few minutes. After accomplishment of the reaction (monitored by TLC) the reaction mixture was poured onto crushed ice and stirred for the separation of molecules. The so obtained solid product was filtered and purified by recrystallization with suitable solvent. (Scheme-1)

**Method B:** To a mixture of o-hydroxy acetophenone (0.01 mol) and hydrazine hydrate (0.02 mol) taken in a mortar was added a catalytic amount of stannous chloride dihydrate, the reaction mixture was grinded with a pestle. Reaction was completed within a couple of minute (TLC). Ice cold water was added to the reaction mixture with shaking. The separated solid was filtered and recrystallized with suitable solvent. (Scheme-2)

The physical data of the synthesized compounds is mentioned in Table-1.

## EXPERIMENTAL

All chemicals were purchased from S. D. fine Chemicals (India). Melting points were recorded using open capillary method and are uncorrected. The progress of the reaction was monitored by thin layer chromatography technique. IR spectra were recorded on Perkin-Elmer 237 spectrometer.  $^1\text{H}$  NMR spectra on Bruker Avance DPX400 MHz spectrometer with  $\text{CDCl}_3$ / DMSO as solvent and TMS internal standard. The chemical shift values are expressed in part per million (ppm).

**Table-1. Physical data of the synthesized compounds**

Sr.No.	Carbonyl Compounds (1)	Hydrazine	Product (3)	Yield (%)	M.P. ( <sup>o</sup> C)
a		NH <sub>2</sub> .NH <sub>2</sub> .H <sub>2</sub> O 2		98	65-68
b		2		91	99-104
c		2		93	160-162
d		2		85	210-213
e		2		82	156-158
f		2		84	119-122
g		2		90	84-86
h		2		81	124-126
i		2		92	75-78
j		2		98	89-91
k		2		87	>250

l		2		89	140-142
m		2		90	200-203
n		2		92	145-148
o		2		95	142-145

Table-2. Optimization of the catalyst for the synthesis of hydrazones

Entry	SnCl <sub>2</sub> ·2H <sub>2</sub> O (mmol)	Time (Min)	Yield (%)
1	0.1	2	98
2	0.2	2	97
3	0.4	2	95
4	0.6	2	95
5	0.8	2	96

### Spectral analysis of representative molecules

**1. 2,4-Dibromo-6-hydrazonomethyl-phenol (3c):** IR (KBR)  $\nu$ : 3396 (O-H), 3287 (N-H), 3073 (Ar C-H), 1625 (C=N), 1369, 1213 (C-O)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\delta$  ppm): 12.45 (s, 1H, OH), 7.7 (s, 1H, CH=N), 7.1-7.4 (m, 2H, Ar-H), 6.90 (s, 2H, NH<sub>2</sub>). Mass (ESI)  $m/z$ : 294.

**2. 2-(1-Hydrazono-ethyl)-4, 6-diiodo-phenol (3f):** IR (KBR)  $\nu$ : 3379 (O-H), 3290 (N-H), 2940 (Ar C-H), 1590 (C=N), 1382, 1185 (C-O)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\delta$  ppm): 14.06 (s, 1H, OH), 7.5-7.9 (m, 2H, Ar C-H), 6.39 (s, 2H, NH<sub>2</sub>), 2.20

(s, 3H, CH<sub>3</sub>), 2.21 (s, 3H, CH<sub>3</sub>). Mass (ESI)  $m/z$ : 402.

**3. 2-Bromo-6-(1-hydrazono-ethyl)-4-methyl-phenol (3o):** IR (KBR)  $\nu$ : 3385 (O-H), 3310 (N-H), 2948 (Ar C-H), 1604 (C=N), 1370, 1213 (C-O)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\delta$  ppm): 14.07 (s, 1H, OH), 7.1-7.18 (m, 2H, Ar C-H), 6.47 (s, 2H, NH<sub>2</sub>), 2.24 (s, 3H, CH<sub>3</sub>), 2.15 (s, 3H, CH<sub>3</sub>). Mass (ESI)  $m/z$ : 243.

### CONCLUSION

In conclusion we have developed an expedient synthesis of hydrazones with promotion to green chemistry principles at

the cost of economical catalytic system. The promising feature of this methodology is the short reaction time and atom efficient grinding technique.

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